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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,791	10/25/2000	Joan M. Robbins	480124.407	4714

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EXAMINER
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/696,791	ROBBINS ET AL
	Examiner	Art Unit
	Karen A. Lacourciere	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-79 and 85-109* is/are pending in the application.

4a) Of the above claim(s) *79 and 109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-78 and 85-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4)☒ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group L in Paper No. 10 is acknowledged.

Applicant's amendments filed 07-22-2002 add new claim 109, which is drawn to a separate invention than the elected invention. Claim 109 is drawn to a nucleic acid sequence, which is capable of use in a materially different method than the method of elected invention. For example, the nucleic acid of claim 109 can be used in an in vitro method of cleaving a nucleic acid sequence, which is materially different than the method of treating a proliferative eye disease of group L.

Claims 79 and 109 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Applicant's amendments filed 07-22-2002 add new claims 106-108, which will be examined as part of the elected Group, however, these claims are drawn to multiple specific sequences and, therefore, a further election is required, as follows:

Pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the antisense sequences listed in claims 106-108 are subject to restriction. The Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of such nucleotide sequences to be claimed in a single application. Under this policy, up to 10 of independent and distinct nucleotide sequences will be examined in a single application. (see MPEP 803.04 and 2434)

Claims 106-108 specifically claim ribozyme SEQ ID NOS 3855-4115, 4143-4152 and 4381-4385, which are targeted to and inhibit the expression of PCNA cyclin. Although the ribozyme sequences claimed each target and modulate expression of the same gene, the instant sequences are considered to be unrelated, since each ribozyme sequence claimed is structurally and functionally independent and distinct for the following reasons: each ribozyme sequence has a unique nucleotide sequence, each sequence targets a different and specific region of a nucleic acid encoding PCNA cyclin, and each ribozyme, upon binding to a nucleic acid encoding PCNA cyclin, functionally modulates the expression of the gene to a varying degree. Furthermore, a search of more than one (1) of the sequences claimed in claims 106-108 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences. In view of the foregoing, one (1) sequence is considered to be a reasonable number of sequences for examination. Accordingly, applicants are required to elect one (1) sequence from claims 106-108.

During a telephone conversation with David Spolter on 09-20-02 a provisional election was made with traverse to prosecute the invention of Group L with the additional election of ribozyme sequence SEQ ID NO: 4145. During this telephone conversation, Mr. Spolter stated that SEQ ID NO: 4145 is the target sequence of the claimed ribozyme and that ribozyme sequences SEQ ID NO: 4381-4385 are ribozymes which target that site and comprise the complement of SEQ ID NO:4145 and that a search for SEQ ID NO:4145 would provide a search for each of SEQ ID NO:4381-4385

and should be examined along with SEQ ID NO:4145 as part of the elected invention. SEQ ID NO:3855-4115, 4143, 4144 and 4146-4152 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

In summary, Group L, claims 71-78 and 85-108, target sequence 4145 and ribozyme sequences 4381-4385 will be examined on the merits. Claims 79 and 109 and SEQ ID NO: 3855-4115, 4143, 4144 and 4146-4152 are withdrawn from further consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 85, 86, 107 and 108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 85 and 86 are indefinite because there is no antecedent basis for the term "nucleic acid" in claim 71.

Claim 107 is indefinite due to the recitation "selected from the group consisting of and 4381 to 4385". It is unclear what the members of the group consist of due to the term "and", for example, are there other, unspecified members of the group? Claim 108 is indefinite for the same reasons due to dependence on claim 107.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71-78 and 85-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating proliferative vitreoretinopathy (PVR) by intravitreally injecting a ribozyme consisting of SEQ ID NO: 4385, does not reasonably provide enablement for treating generally any proliferative eye disease using a ribozyme targeted to a PCNA encoding nucleic acid comprising SEQ ID NO: 4145, or for treating a proliferative eye disease using a vector expressing a ribozyme, or treating PVR using any ribozyme other than SEQ ID NO: 4385. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the

nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 71-78, and 85-108 are drawn broadly, and would encompass methods of treatment for a broad class of eye disorders with a broad range of underlying biological cause. For example, the claims include particular limitations wherein the disorder is various forms of retinopathy, diabetic, vitreoretinopathy, sickle cell retinopathy and retinopathy of prematurity, however, the broad term "proliferative eye disorder" would include disorders like scarring on the eyelid and melanoma on the eyelid. Additionally, the methods claimed would broadly encompass using any ribozyme targeted to a nucleic acid comprising SEQ ID NO:4145 encoding PCNA, delivered by any means, including systemic administration.

The specification provides one example, wherein a dispase induced rabbit model of PVR is treated using an intravitreally injected ribozyme consisting of SEQ ID NO: 4385 or 4383 (example 8). In the one example provided, SEQ ID NO 4385 results in a significant improvement for PVR (see Table 23), however, SEQ ID NO: 4383 does not appear to provide the same treatment effect (for example, SEQ ID NO:4383, PN30004, has an average score of 3.1±1.3, a range of 1.8 to 4.4, and controls are ranges of 3.5 to 6.5, or even as low as 2.5±0.7, 2.2±0.4). The specification does not provide any examples or guidance on treating any disorder besides PVR in vivo, nor does it provide any guidance on delivery of a ribozyme by any means besides intravitreal injection, nor

does it provide any guidance on methods of treatment using a ribozyme delivered using a vector.

At the time the instant invention was made, the therapeutic use of oligonucleotides, including ribozymes, and gene therapy methods (eg. vector expressed ribozymes) was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of oligonucleotides *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch (TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Theses references are directed mainly to antisense considerations, however, these obstacles would also apply to ribozymes. Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable, non-specific effects. Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of oligonucleotides for in vivo therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense

ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein on ribozyme is effective when provided by local administration, however, this example does not provide guidance for generally any ribozyme, or for systemic delivery, due to differences in metabolites and clearance rates, local concentration, differences in target site accessibility, cellular uptake differences and the potential for non-specific effects. For example, on page 29 of the specification, the specification demonstrates how several ribozymes have very different half-lives in serum and in cell lysate, due to only small differences in modifications of each ribozyme. This difference in half-life would have a large impact on the efficacy of a ribozyme in vivo. Additionally, difference in sequence and modification would cause each ribozyme to have a varying binding rate to the target molecule, and a different cellular uptake, which would have a large impact on in vivo efficacy. For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and

sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Due to differences in the uptake and binding activity for an individual ribozyme, the efficacy observed for SEQ ID NO: 4385 would not predictably translate to *in vivo* results for any other ribozyme, as supported by the large difference seen between SEQ ID NO:4383 and 4385.

Additionally, the claimed methods are drawn to methods wherein a vector expressing a ribozyme is used in the claimed methods of treatment, which would encompass gene therapy methods. The specification does not disclose any methods wherein an expressed ribozyme is used to treat a proliferative eye disease. At the time of the instant invention and even to date, gene therapy methods were highly unpredictable (see, for example, Verma et al. or Anderson, W.F.), and had many of the same problems as discussed for antisense and ribozymes, in that the it was difficult and unpredictable to deliver an effective amount of a vector specifically to a target cell in vivo (whole organism). Gene therapy methods have additional considerations, for example, vectors can result in unpredictable immune responses that preclude a therapeutic effect and often vectors do not provide a sustained expression level, and expression requires a vector particularly designed for a given cell, for example, vectors require an appropriate enhancer-promoter combination, the determination of which is trial and error for a given cell type (see for example, Verma et al.) The specification provides no guidance on how to practice the claimed methods wherein a vector expressing a ribozyme is used to treat a proliferative eye disease, for example, there is no guidance on how to deliver a vector at an effective concentration, how to provide

sufficient sustained expression to provide a therapeutic effect, what type of vector to use, for example, what type of promoter-enhancer combination would provide an effective expression level. The field of gene therapy does not have specific guidelines by which one skilled in the art can practice the claimed gene therapy methods successfully, nor is this guidance provided in the specification. Therefore, the skilled artisan would need to determine this de novo, through undue trial and error experimentation.

The claimed methods additionally encompass methods wherein a decoy oligonucleotide is delivered in addition to a ribozyme to treat a proliferative eye disease. Dzau (Dzau, V. (Circ. Res. 2002; 90:1234-1236.)) discusses the difficulty of using decoy oligonucleotides "The long term success of TFD oligonucleotide as a broadly utilized therapeutic modality will depend on several critical factors. These include the specificity of the TFD, the stability of the oligonucleotide, and the efficiency of tissue/cellular delivery...Another major determinant of TFD effect is the efficiency of cellular uptake and delivery...Finally the timing of treatment with TFD may also be important in influencing the therapeutic effect." (see Dzau, p 1235, firs column). As Dzau points out, various strategies employed to overcome these hurdles have met with varied success. As claimed, the treatment methods would require the delivery of an effective concentration of two different oligonucleotides, each of which are unpredictable to deliver in vivo (whole organism). The specification has not provided any specific decoy oligonucleotides that are effective to treat a proliferative eye disease, nor has the specification provided any examples or specific guidance by which the skilled artisan

would be able to deliver an effective concentration of a decoy oligonucleotide in vivo (whole organism), nor does the field provide such specific guidelines.

Therefore, to practice the claimed methods of treatment for a proliferative eye disease it would require the skilled artisan to undergo undue trial and error experimentation to practice the claimed methods over the full scope claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere

October 21, 2002